Can Colchicine be a New Captain in Coronary Artery Disease Management? A Systematic Review

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Abstract. Despite the control of the conventional modifiable factors, many patients are still experiencing life-threatening first and recurrent cardiovascular events. Inflammation has a key role in all stages of development and progression of atherosclerosis. A detailed understanding of its role and the cellular dynamics, which contribute to atherosclerotic inflammation, is important in finding agents suitable to target it. The recent CANTOS trial highlighted that the interleukin-1b inhibitor canakinumab could improve outcomes after acute coronary syndrome; however, being a high and increased risk of infections limited its administration for long-term treatment. Drugs acting on targets outside the interleukin-1b pathway failed to show clinical benefits. The most likely emerging anti-inflammatory agent low-dose colchicine is an affordable, safe, and more accessible alternative. This review aims at highlighting the role of inflammation in atherosclerosis and coronary artery diseases and the role of colchicine, an anti-inflammatory agent in patients with coronary artery disease, including both stable coronary artery disease and acute coronary syndrome.

To cite this article
[Kumar, P., Khan, S., Gordon, D. K., Hussain M. & Khan, S. (2020). Can Colchicine be a New Captain in Coronary Artery Disease Management? A Systematic Review. *The Journal of Middle East and North Africa Sciences*, 6(10), 10-18]. (P-ISSN 2412- 9763) - (e-ISSN 2412-8937). www.jomenas.org. **3**

Keywords: Colchicine, Inflammation & Atherosclerosis, Inflammation & Coronary Artery disease, Colchicine & Atherosclerosis, Colchicine & Myocardial infarction, Colchicine & Acute coronary syndrome

1. Introduction:

Coronary heart disease is the leading cause of morbidity and mortality in the US, accounting for 42.6% of all deaths attributable to cardiovascular cause and overall, 13% deaths in 2017. Approximately every 40 seconds, an American will have a heart attack (Benjamin et al., 2019). American Heart Association introduced the strategy of "Life simple 7" which included tracking of key risk factors for heart disease and stroke including smoking, physical activity, healthy body, weight and control of cholesterol, Blood pressure and blood sugar (Roger et al., 2012). Despite the control of these conventional modifiable factors, many patients are still experiencing life-threatening first and recurrent cardiovascular events.

The central to the pathophysiology of coronary artery disease is atherosclerosis. The three vital factors that interplay the role in the pathogenesis of atherosclerosis are- Dyslipidemia, Hemostasis, and Inflammatory response. Cholesterol crystals cause endothelial activation, which triggers the release of pro-inflammatory cytokines like interleukins (IL0 such as IL1B, IL6, IL18. Inflammation is involved at all stages of atherosclerosis from plaque formation, progression, instability, and rupture (Loscalzo 2004; Peter et al., 2004).

Inflammation measured by high sensitivity C-reactive protein (hs-CRP) and IL6 levels is strongly associated with future vascular events in both primary and secondary prevention (Scalera et al., 2005). Statins, used traditionally in medical management, also has pleiotropic anti-inflammatory property along with its lipid-lowering action. But the trials failed to conclude the lowering of cardiovascular events was due to altering inflammation (decreased CRP) or clinical response to lowering of lipid levels (decreased LDL) (Ridker et al., 2008).

Over the past two decades, there has been growing interest in the search and development of novel anti-inflammatory drugs targeting various known inflammatory factors. However, most of them failed to demonstrate clinical benefits in large randomized trials (Rymer & Newby, 2017).

Canakinumab, a humanized monoclonal antibody against IL-1B approved for the rheumatological disorder, was considered. IL-1B, a pro-inflammatory cytokine, plays multiple roles in atherogenesis, plaque growth, and subsequent rupture. It is involved in the promotion of monocyte and leukocyte adhesion to endothelial cells, proliferation of vascular smooth muscle cells, and

procoagulant activity induction. A significant randomized phase-3 trial, CANTOS in patients with myocardial infarction and raised hs-CRP level showed a substantial reduction in the primary endpoint, which was very well accompanied by a decrease in hs-CRP levels without any significant reduction in lipid levels from baseline. However, the drug was costlier, and there was no significant reduction in mortality. Besides, a significantly higher incidence of fatal infection and sepsis with a reduction in platelet counts and neutropenia was noted with canakinumab (Ridker et al., 2017). Its modest clinical advantage could not justify its routine use due to safety and affordability factors. Simultaneous to CANTOS another trial- the Cardiovascular Inflammation Reduction Trial (CIRT) was started with low dow dose Methotrexate in patients with previous ACS or multivessel coronary artery disease. Methotrexate failed to lower the IL-1B, IL-6, and CRP and also did not result in fewer cardiovascular events than placebo (Ridker et al., 2019).

More affordable and tolerable alternatives to canakinumab are being evaluated recently. Of these, colchicine has emerged as a potentially useful anti-inflammatory agent. Colchicine initially extracted from the autumn crocus is being used over centuries for gout. It is also indicated for pericarditis and familial Mediterranean fever. Apart from its classic anti mitotic action, colchicine acts at many other levels in the inflammatory cascade, including cellular adhesion molecules, inflammatory chemokines, and the NOD-like receptor protein 3(NLRP3) inflammasome (Deftereos et al., 2013). Following exposure to an irritative stimulus, the NLRP3 inflammasome converts pro-IL-1ß to active IL-1ß. Cholesterol crystals can trigger inflammasome assembly by causing direct trauma to the vessel wall.

Similarly, in gout, the uric acid crystals initiate an inflammatory cascade. Retrospective studies have shown a decreased incidence of ischemic heart diseases as well as other cardiovascular diseases in patients who were on continuous colchicine treatment for gout and familial Mediterranean fever (Crittenden et al., 2012). Initial studies of colchicine in patients with stable coronary heart disease have been promising. Recent shreds of evidence suggesting the role of low dose colchicine in reducing cardiovascular events and the low risk of significant side effects have been described in the Low-Dose Colchicine (LoDoCo) trial in patients with stable coronary disease and the COLCOT trial in patients who recently had MI. This review article outlines the anti-inflammatory action of colchicine. It details the past studies to examine how and why colchicine has the potential to become a cornerstone anti-inflammatory therapy in the management of coronary heart diseases.

2. Literature Search:

An extensive literature search was performed using specific terms in the PubMed search to find related published articles as well as in the clinical trial registries to identify finished and ongoing clinical studies. Keywords such as “colchicine,” “coronary artery disease,” “atherosclerosis,” “acute coronary syndrome,” “inflammation” were used alone and in combination.

Table 1 represents the results of the keywords used alone and in combination. References of relevant articles were also reviewed and selected.

Keyword	Number of articles in PubMed
Colchicine	21,393
Inflammation & Atherosclerosis	22,803
Inflammation & Coronary Artery disease	7,549
Colchicine & Atherosclerosis	106
Colchicine & Myocardial infarction	100
Colchicine & Acute coronary syndrome	42

3. Discussion:

Despite the contemporary measures for control of cardiovascular risk factors including smoking cessation, exercise, dietary modification, blood pressure control, anti-lipid agents, and antithrombotic agents, coronary artery disease (CAD) causing acute coronary syndrome (ACS) are leading causes of morbidity and mortality across the globe. There is increasing evidence supporting inflammation as a process central to all the stages of atherosclerotic plaque development, progression, instability, and rupture leading to acute clinical events. The rate of recurrent events 30 days post index ACS is estimated to be around 2% (Tobbia et al., 2013; Brieger et al., 2009), and up to 20% at three years [Martínez et al., 2018; Ideker & Huang, 2005). The residual coronary inflammation acts as one of the major contributory factors (Angiolillo et al., 2004).

3.1. Role of inflammation in coronary artery diseases:

Understanding the molecular and cellular mechanisms allows the identification of novel anti-inflammatory therapeutic targets and helps in prognostic stratification (Tousoulis et al., 2016). Since the innate and adaptative immune responses both play a crucial part in atherogenesis (Hansson, 2002), it is hence now considered as cholesterol crystals and other stimuli that triggered chronic inflammation (Peter at al., 2004).

The critical effectors of the inflammatory response throughout the atherosclerotic disease process are monocytes/macrophages. Endothelial cell adhesion molecules initiate the recruitment of monocytes, followed by chemokine-guided migration into the arterial intima

(Czech & Hannon, 2011). The recruitment of monocytes is present in both early as well as mature lesions suggesting their role throughout the development of plaque. Further through the scavenger receptor A and CD3, they engulf oxidized Low-Density Lipoproteins (LDL), transforming into foam cells. This is associated with the release of several cytokines, most importantly, interleukin-1β (IL-1β) and TNF-α (Stewart et al., 2009), promoting further recruitment of leukocytes. Later the release of metalloproteinases from macrophages may promote destabilization of the plaque through collagen mediated fibrous cap weakening, which can result in rupture of plaque and fresh.

Polymorphonuclear neutrophils are also important contributors to inflammation and plaque destabilization as they accumulate in the most rupture-prone regions of the plaque (Carbone et al., 2015; Martínez et al., 2017). Cholesterol crystals activated neutrophils can also expel neutrophil extracellular traps (NETs), web-like structures containing DNA, histones, neutrophil elastase, myeloperoxidase. The metalloproteinases like proteinase-3 secreted by PMN can degrade the constituents of the fibrous cap. Elastase is capable of cleaving almost all components of the extracellular matrix. Myeloperoxidase (MPO) helps in promoting lipid peroxidation, resulting in oxidized lipids, which are engulfed by macrophages, inducing foam cell formation. MPO can further activate metalloproteinases initiating plaque disruption by the production of reactive oxygen species (ROS) (Mazor et al., 2008).

3.2. Role of NLRP3 inflammasome:

The innate immune response utilizes pattern-recognition receptors (PRRs), including the inflammasomes. The nucleotide-binding domain, leucine-rich family, pyrin containing domain 3 (NLRP3/NOD like receptor 3) inflammasome is cytoplasmic. It is present in monocytes, neutrophils, and eosinophils. It comprises the NLRP3 receptor, which is the Toll-like receptor, the adaptor protein apoptosis-associated speck-like protein containing caspase, and activation recruitment domain (CARD)-ASC and the cysteine protease caspase-1 (Franchi et al., 2008). The inflammasome activation is a two-step process with priming by Toll-like receptor stimuli or by monocyte induced activation of nuclear factor kappa B (NF-κB)- mediated signaling, prompting transcription of components (Warnatsch et al., 2015). Further, the stimuli promote assembly of inflammasomes and activation of caspase-1, ultimately inducing the production of mature cytokines like IL-1β. It is increasingly being recognized that macrophages that have phagocytosed and accumulated cholesterol crystals can stimulate the inflammasome complex and cytokine production. Cholesterol crystals present in higher concentrations in unstable plaques correlate with higher inflammasome activity in such lesions. Warnasch et al. demonstrated that within the atherosclerotic plaque, NETs closely co-locate with macrophages. They prime macrophages to produce pro–IL-1β, which is converted to mature form by NLRP3 inflammasome (Bujak et al., 2008). These pieces of evidence highlight the role of the NLRP3 inflammasome in atherosclerosis and prompt the search for novel therapies against this complex.

3.3. Role of cytokine Interleukin 1b:

IL-1b is now considered as a critical atherogenic inflammatory cytokine. It acts by promoting the adhesion of leukocytes to vascular endothelial cells, the proliferation of vascular smooth muscle cells, and enhancing the procoagulant factors (Rymer & Newby, 2017; Ridker et al., 2017). It contributes to the acute phase response by stimulating the IL-6 receptor signaling pathway. IL-1β also hinders the post-MI cardiac remodeling by stimulating post-MI apoptosis and fibrosis. Hence we can reduce myocardial dysfunction after MI by inhibiting IL-1β activity (Ridker et al, 2005).

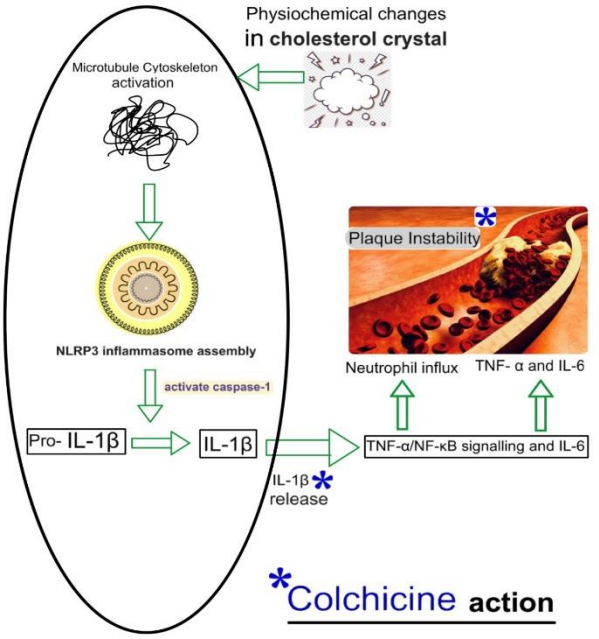

Figure 1. Various sites of action of colchicine significant to atherosclerosis. NLRP3, NOD-, LRR- and pyrin domain-containing protein 3; IL-1ß, interleukin-1ß; TNFa, tumor necrosis factor-a; IL-6, interleukin-6.

3.4. Novel Anti-inflammatory Drugs:

The ability of novel anti-inflammatory drugs to modify this inflammatory response has been the subject of recent research. Statins with their lipid-lowering properties are known to have pleiotropic anti-inflammatory properties. They inhibit T-cell activation, macrophage infiltration, and leucocyte adhesion, and also reduce reactive oxygen species generation. Many clinical trials

have demonstrated improvement in clinical outcomes due to a reduction in hs-CRP with statin therapy, which is independent of its lipid-lowering action (Nissen, 2005; Bohula et al., 2015). The Pravastatin or Atorvastatin Evaluation and Infection Therapy trial (PROVE-IT) with moderate or intensive lipid-lowering statin therapy in ACS found that ACS patients with CRP level <2 mg/L after statin therapy had a lower rate of recurrent MI or death due to CAD than those with higher-level (Nissen, 2005). Similar results were found in the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) (Giugliano et al., 2003). Further JUPITER trial (Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin) also demonstrated that statin resulted in a lower risk of cardiovascular events among patients with an elevated level of hs-CRP. However, it cannot be concluded that the anti-inflammatory effect was solely responsible for the clinical benefit as LDL cholesterol was also lowered from baseline [6]. Corticosteroids were then investigated as anti-inflammatory therapy after ACS. A

A meta-analysis of 11 trials demonstrated a 26% decrease in mortality; however, on sensitivity analysis limited to extensive studies and randomized trials found a lack of efficacy (Olsen et al., 2012). Due to a possible concerning the effect of steroids on impaired wall healing after MI, resulting in cardiac rupture, steroids were then abandoned.

On the evaluation of Nonsteroidal anti-inflammatory drugs, it was found that they increased the risk of recurrent MI and mortality in patients for five years post-MI (Papageorgiou et al., 2017). Another anti-inflammatory agent methotrexate was evaluated in the Cardiovascular Inflammation Reduction Trial for the effect of low-dose methotrexate (target dose, 15-20 mg/week) in improving cardiovascular outcomes among patients with prior MI or multivessel coronary artery disease. However, it did not reduce levels of interleukin-1β, interleukin-6, or C-reactive protein and did not result in fewer cardiovascular events than placebo among patients with stable atherosclerosis (Ridker et al., 2019). It was also associated with side effects like leucopenia, deranged liver enzymes, and increased risk of non–basal-cell skin cancers.

Recently more specific novel anti-inflammatory agents like Pexelizumab, Varespladib, Inclacumab, Darapladib, and losapimod targeting various steps in the inflammatory cascade have been studied. But, most of them failed to demonstrate therapeutic benefits in large RCTs.

Canakinumab, a humanized monoclonal antibody against interleukin-1β, is approved for use in systemic juvenile idiopathic arthritis and cryopyrin-associated periodic syndromes. CANTOS trial was designed to test the inflammatory hypothesis of atherothrombosis directly. In the trial, in patients with a history of myocardial infarction, the levels of his CRP was significantly reduced from baseline by canakinumab. The primary endpoint was 15% lower and the Secondary cardiovascular endpoint that was 17% lower than that in the placebo group (Ridker et al., 2017). Reduction in CVS events was significant (hazard ratio, 0.85); the disconcerting results included an increased risk of fatal infection and no mortality benefit. Also, the drug is expensive ($200,000 per year). Hence the modest clinical benefit does not justify its routine clinical use unless efficacy, safety, and cost-effectiveness are proved.

An ideal candidate therapy also must be well-tolerated, have no long-term side effects, be readily available and inexpensive, and have potential actions at the level of the atherosclerotic plaque. Of the agents currently available, low doses of the widely available colchicine fulfill many of these criteria.

3.4. Role of Colchicine:

Colchicine, an anti-inflammatory agent, used for centuries for gout acts by inhibition of tubulin polymerization and microtubule generation and possibly has effects on cellular adhesion molecules, inflammatory chemokines, and the NLRP3 inflammasome. It promotes microtubule depolymerization by binding to tubulin and also inhibits the activation of the NLRP3 inflammasome (Deftereos et al., 2013). It has also been utilized in the treatment of perioperative atrial fibrillation and pericarditis (Lee et al., 2013).

Its mechanism of action of inhibiting NLRP3 inflammasome and hence IL1 and IL6 can be used in atherosclerosis. Recently there have been extensive studies with regards to multiple sites of action of colchicine in the inflammatory cascade (Misawa et al., 2013). Its action of binding to tubulin contributes to its ability to affect a variety of multiple cellular actions, including NLRP3 inflammasome assembly inhibition (Apostolidou et al., 2016). Mechanisms by which activation pf NLRP3 inflammasome is suppressed by colchicine include direct monocyte caspase-1 inhibition, inhibition of co-localization of inflammasome cytoplasmic proteins, inhibition of P2 × 7-mediated pore formation in response to ATP and inactivation of the MEFV gene. In addition to its effect on neutrophils, colchicine impairs the release of IL-1b into NETs (Robertson et al., 2016). In patients with ACS when the ex-vivo monocytes received short-term colchicine therapy, there was a marked reduction in intracellular and secreted levels of IL-1b compared with pretreatment levels. There was also a significant reduction in procaspase-1 mRNA levels and secreted caspase-1 protein levels, which thereby led to a reduction in IL-1b secretion with short term colchicine therapy (Colchicine, 2020).

The adverse effects associated with colchicine therapy commonly include diarrhea, nausea, vomiting. Othe rare adverse effects are blood dyscrasias, hepatitis, hypersensitivity reactions, and rhabdomyolysis. It also interacts with other drugs with CYP3A4 inhibitory action,

statins, and calcineurin inhibitors like tacrolimus. It should be cautiously used in patients with renal disease, hepatic disease, and pregnancy (Deftereos et al., 2013).

Low-dose long-term colchicine therapy has been used in patients with Familial Mediterranean Fever with doses up to 2.4mg daily as approved by the FDA (Robertson et al., 2016). Extensive population-based studies in FMF patients acts as a surrogate clinical model for the role of chronic inflammation in the development of vascular disease and the safety of long-term anti-inflammatory therapy with low-dose colchicine for its prevention. In a study with 4,000 patients with untreated FMF, there was a risk factor for premature coronary disease, and patients with FMF who developed the coronary disease were more likely to have a pro-inflammatory genotype of the FMF gene.

Martınez et al. studied for the first time the in vivo effects of oral colchicine on cardiac production of inflammatory cytokines. In 40 patients with ACS and 33 with stable coronary artery disease patients, colchicine was administered in a dose of 1 mg, followed by 0.5 mg after 1 hour (Sun et al., 2009). IL-1b, IL-6, and IL-18 levels in coronary sinus were significantly more than artery and vein (p=0.017) in fresh ACS patients. These findings suggest cholesterol crystal-induced inflammation within atherosclerotic plaque initiates plaque instability. Hence supporting the role of low-dose colchicine in improving patient outcomes by NLRP3 inflammasome inhibition (Sun et al., 2009).

3.5. Role of Colchicine in stable coronary artery disease

Mark Nidorf conducted a pilot study to investigate the effect of low-dose colchicine in patients with stable coronary artery disease having hs-CRP more than 2.0 mg/L and on optimum medical treatment including aspirin and statin (Nidorf et al., 2013). Hs-CRP was repeated after two weeks in the non-treatment group and after four weeks in the treatment group. Colchicine significantly ($p < 0.001$) reduced hs-crp from 4.58±2.05 to 1.78±1.38 mg/L. The relative reduction was found to be 60%. Additionally, it was observed that hs-CRP levels decreased by >50% from baseline in 64% of patients and to <2.0 mg/L in 70% of patients (Nidorf et al., 2013). There was no significant reduction in hs-CRP levels in the non-treatment group. There were no associated considerable side effects.

Nevertheless, caution needs to be taken in the interpretation of this study as it was small, short term, and non-randomized. However, the quick follow-up was purposely chosen because it was considered that if therapy indeed was active, it should be apparent early and because of concern that should patients in the treatment group develop an intercurrent illness during the observation period, any effect of treatment would have been missed. It led to the first LoDoCo (Low-Dose Colchicine) trial, which also evaluated the effect of colchicine in patients with stable coronary disease who were on optimal medical therapy and recruited without reference to baseline levels of hs-CRP (Raju et al., 2012). Five hundred thirty-two patients with stable CAD receiving aspirin and/or clopidogrel (93%) and statins (95%) were randomly assigned to colchicine 0.5 mg/day or no colchicine. They were followed up for a median of 3 years. It was found that colchicine was effective in the prevention of primary outcome events (HR 0.33, P <0.001) compared with placebo. The primary outcome consisted of cardiovascular death, acute coronary syndrome non-cardioembolic stroke, and out-of-hospital cardiac arrest. This pragmatic trial provided the first clinical data on the efficacy of colchicine as a strategy of secondary prevention in stable coronary artery disease.

3.6. Role of Colchicine in Fresh ACS

Studies are demonstrating the role of colchicine in the setting of acute coronary events like plaque rupture. A small initial study was conducted by Raju et al., with 80 patients who had ACS or acute ischemic stroke. They were followed up for 30 days. It was found that there is no difference in hsCRP or platelet aggregation in the trial group as compared to placebo (Deftereos et al., 2015). One of the shortcomings in the study was that it was not specified in the study about the timing of colchicine administration after fresh ACS. The acute inflammatory processes would have subsided after 30 days of index event even in the control group rendering these findings difficult to interpret. Deftereos et al. conducted a trial in 151 patients presenting with STEMI (treated with PCI). They were randomized either to colchicine (loading dose of 2 mg then 0.5 mg BD) or placebo for five days to test the hypothesis of the possible reduction in infarct size with a short course of colchicine (Vaidya et al., 2017). It was found that the area under the curve for CK-MB was nearly half that of the placebo group ($P < 0.001$). Cardiac magnetic resonance imaging (CMR)-defined infarct size and the relative infarct size as a proportion of left ventricular myocardial volume were smaller in the colchicine group. These results demonstrate the role of short-term colchicine in reducing infarct size in MI patients having been treated with PCI.

Further, a prospective study by Vaidya et al. in 80 patients with recent ACS, used computed tomography coronary angiography at baseline and 12 months to evaluate change in low attenuation plaque (LAP) volume as the primary outcome and other computed tomography coronary angiography parameters, including total atheroma volume as secondary outcomes along with hsCRP level (Huynh, 2020). During the 12 months, there was a significant mean reduction in LAP volume of 41% in the treatment group as compared to 17% in the control group. Similarly, there was a significant reduction in hsCRP levels in both treatment group and controls groups (37% and 15% respectively) from baseline with a compelling statistically significant difference ($p < 0.0001$)

between the two groups. The changes in LAP volume were in positive correlation with the change in hsCRP level on linear regression analysis. Also, these changes were seen independent of substantial reductions in LDL cholesterol (p= 0.21) and total atheroma volume (p= 0.28), which were comparable in both groups (Huynh, 2020). This study added strong evidence on the use of regular low-dose colchicine therapy as a substantially more powerful coronary plaque stabilizing effect than OMT alone.

Jean-Claude Tardiff et al., conducted the Colchicine Cardiovascular Outcomes Trial (COLCOT) to demonstrate the effects of colchicine on cardiovascular outcomes and its long-term safety in 4745 patients who had MI within the preceding 30 days. They were on optimum medical treatment with having a percutaneous coronary intervention, as indicated. The trial group was given 0.5mg colchicine daily and followed up for a median of 22.6 months. A composite of resuscitated cardiac arrest, myocardial infarction, cardiovascular deaths, stroke and unstable angina leading to urgent hospitalization was considered as the primary endpoint, and it occurred in 5.5% of patients in the trial group as compared to 7.1% in the placebo group (p>0.02) (ANZCTR, 2020). It was associated with a slight increase in pneumonia and no significant difference in diarrhea. The benefit in this trial was mainly driven by a decrease in the rate of stroke and angina, leading to emergency hospital admission and revascularisation. However, it is crucial to observe that despite the impressive reduction in the primary composite endpoint, cardiovascular death, or myocardial infarction as individual endpoints were not significantly reduced. Also, the duration of follow-up was relatively short, being approximately 23 months. The risks and benefits of long-term treatment with colchicine were not observed and evaluated.

Currently, new Phase III clinical trials examining the effect of low-dose colchicine in patients with coronary artery disease are coming up. The LoDoCo2 trial from Australia and the Netherlands, investigated colchicine 0.5 mg in patients with stable coronary artery disease before enrolment for secondary prevention of cardiovascular disease (ClinicalTrials.gov, 2017). Two-Phase III trials The CLEARSYNERGY (Colchicine and Spironolactone in Patients With STEMI/SYNERGY Stent Registry) trial and The CONVINCE (Colchicine for Prevention of Vascular Inflammation in Non-cardio Embolic Stroke) trial of colchicine in patients with atherosclerosis have started recruiting patients. The CLEARSYNERGY study using a two × two factorial design aims to investigate the long-term effects of colchicine 1 mg/d versus spironolactone or placebo in 4000 patients following primary PCI to treat recent ST-elevation myocardial infarction (ClinicalTrials.gov, 2016). This study design addresses the culprit artery by stenting as well as the non-culprit arteries by colchicine and spironolactone administration. The CONVINCE (Colchicine for Prevention of Vascular Inflammation in Non-cardio Embolic Stroke) trial aims to investigate the effect of colchicine 0.5 mg daily on cardiovascular outcomes in patients with previous symptomatic cerebrovascular disease (ANZCTR, 2016). The primary endpoint in both trials comprises of cardiovascular death, myocardial infarction, and stroke. Another upcoming study on the use of colchicine in fresh ACS patients is the COLCARDIO-ACS Study (The effect of Colchicine on Cardiovascular Outcomes in Acute Coronary Syndrome). In this study, around 3000 ACS patients with hb-CRP>2mg/L will be given colchicine 0.5mg daily over the optimal medical therapy for a median of 3 years (ANZCTR, 2016).

4. Conclusion:

Contemporary evidence indicates the central role of inflammation in the development and progression of atherosclerosis. This opens a great field for research on new strategies for treatment in coronary artery disease. Multiple novel anti-inflammatory therapies for ACS and atherosclerosis have been investigated in the last two decades to improve patient outcomes. Colchicine has recently gained importance in secondary prevention in both stable coronary artery disease as well as ACS. Its effect of dampening the inflammatory milieu that potentiates plaque instability, rupture, and atherothrombosis contributes to the reduction of the rate of recurrent cardiovascular events and improving patient outcomes. Furthermore, low dose colchicine is safe in long-term use in various cardiovascular conditions. With more and more trials in the upcoming future, the evidence contributing to the additive role of this low cost, anti-inflammatory drug over the optimum medical therapy in the prevention and treatment of CAD and its sequelae of ACS will be confirmed.

Conflict of Interest:

There was no conflict of interest by authors.

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Received August 13, 2020; reviewed September 01, 2020; accepted September 18, 2020; published online October 01, 2020